Research Article

Immunoinformatical approach of Epitope based vaccine design for Dengu fever virus

Nandhini C, Vijiya Dharshini V and Tamil Bharathi V*

Department of Biotechnology, Vivekanandha College of arts and Sciences for Women (Autonomous), Elayampalyam, Tiruchengode, Tamilnadu, India.

*Correspondence: tamilbharathi1807@gmail.com (TBV)

Abstract : Dengue virus (DENV) outbreaks are a major public health concern in India, necessitating the development of effective vaccination strategies. Existing dengue vaccines have limitations, such as incomplete protection against all virus serotypes and the risk of enhanced infection upon secondary exposure, driving the exploration of innovative vaccine development approaches. This study employs a combined reverse vaccinology and immunoinformatics approach to design a multi-epitope-based vaccine targeting various proteins of DENV. Computational immune-informatics techniques were utilized to identify B-cell and T-cell epitopes across the DENV genome, aiming to enhance the immune response against DENV infection. Bioinformatics tools were employed to predict epitopes, assess antigenicity, and conduct molecular docking to human HLA alleles. Peptides with the lowest binding affinity for each human allele were selected, and their structures were validated. The study identified promising vaccine candidates, including peptides from the whole genomes of DENV serotypes 1 (IGIGVLLTW), 2 (AAFSGVSWTM), 3 (WDFGSV), and 4 (NLEYTVVVTW). These findings highlight the potential of computational approaches in vaccine design, offering insights into novel strategies for combating DENV and potentially other infectious diseases.

Keywords: DENV-1; epitope based vaccines; immunoinformatics; antigens.

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Introduction

Dengue fever is a mosquito-borne viral infection caused by the dengue virus (DENV), which is a member of the Flavivirus genus in the Flaviviridae family [1]. The virus is primarily transmitted to humans through the bite of infected Aedes mosquitoes, particularly Aedes aegypti and Aedes albopictus [2]. Dengue fever is endemic in tropical and subtropical regions of the world, with an estimated 390 million infections occurring annually, leading to approximately 20,000 deaths, mainly among children [3,4]. One of the major challenges in combating dengue fever is the lack of effective vaccines. Although several vaccine candidates have been developed, including the CYD-TDV vaccine (Dengvaxia) developed by Sanofi Pasteur, these vaccines have shown limited efficacy and safety concerns, particularly in individuals without previous exposure to dengue virus [5,6]. Therefore, there is an urgent need to develop more effective and safer vaccines against dengue fever.

In recent years, immunoinformatics has emerged as a powerful tool for vaccine design [7]. Immunoinformatics is the application of computational methods and bioinformatics tools to study the immune system and design vaccines [8]. One of the key applications of immunoinformatics is the design of

epitope-based vaccines [9]. Epitopes are the specific regions of antigens that are recognized by the immune system, and they play a crucial role in inducing immune responses [10].

Vaccination is considered the most effective way to prevent dengue infections. However, current vaccines have not been entirely successful in preventing outbreaks. An ideal dengue vaccine should provide long-term immunity against all four serotypes of DENV. Epitopes, the regions of antigens recognized by the immune system, are crucial for vaccine design. Epitope-based vaccines can stimulate both cellular and humoral immune responses, offering a potential strategy for inducing pathogen-specific immunity [9]. Computational algorithms are used to predict epitopes, with conserved epitopes being particularly important for vaccine development [11]. The components of DENV, including structural and nonstructural proteins, are key targets for vaccine design [12]. The development of epitope-based vaccines for dengue fever virus using immunoinformatics approaches offers several advantages over traditional vaccine development methods. First, epitope-based vaccines can be designed to induce specific immune responses, minimizing the risk of adverse reactions [13]. Second, epitope-based vaccines are highly specific, targeting only the desired epitopes of the virus. Third, epitope-based vaccines can be designed to target multiple epitopes from different serotypes of dengue virus, providing broad-spectrum protection against dengue fever. The DENV genome is approximately 11,000 bases long and encodes for three structural proteins (capsid protein C, membrane protein M, envelope protein E) and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5) [14-16]. Dengue infections can sometimes lead to severe outcomes like haemorrhagic fever or shock syndrome [17]. Several dengue vaccines are in various stages of development, with only one currently licensed for use. Most of these vaccines are based on the envelope proteins prM and E, which are expected to trigger protective immune responses in humans. However, it's important to note that the human immune response to dengue virus (DENV) is mainly characterized by highly cross-reactive antibodies that can have both neutralizing and enhancing effects.

Dengvaxia, manufactured by Sanofi Pasteur, is a live, attenuated, tetravalent recombinant vaccine known as ChimeriVax [18]. It was the first vaccine licensed for dengue in 2015 due to promising results from various clinical studies [19]. Dengvaxia has been approved by the US FDA for use in areas where dengue is prevalent and is available in 19 countries [20]. However, its use is restricted to certain age groups and cannot be administered to individuals who have not been previously exposed to flaviviruses [21]. One of the concerns with Dengvaxia is its potential to cause severe dengue in individuals who are seronegative at the time of vaccination and later become infected with DENV. This issue was highlighted in a 2018 publication reporting an increased rate of hospitalization among seronegative vaccinated children aged 9-11 [22]. This has led to concerns that Dengvaxia

may not be effective in providing long-term protection and could even enhance the severity of dengue disease in some cases. Another limitation of Dengvaxia is that it does not contain non-structural proteins of DENV.

Immunologically, DENVs are closely related but genetically and antigenically distinct. They share approximately 75% genetic relatedness. DENV is divided into different serotypes based on the envelope gene, which is responsible for incomplete cross-defensive immunity between serotypes in humans. This means that infection or vaccination with one serotype does not provide complete protection against the other serotypes. The development of disease, viral replication, and the immune response are all influenced by the antigenic determinants of DENV proteins. Therefore, identifying antigenic protein sequences that can elicit strong immune responses in the host is crucial for developing effective vaccines against dengue [23].

In this study, we utilized computational approaches to design multiple epitope-based vaccines against Dengue Virus (DENV). These vaccines are composed of multiple epitopes that can activate cytotoxic T lymphocytes (CTLs) and helper T lymphocytes (HTLs), key components of the immune system. Unlike traditional vaccines that use pathogens or attenuated viruses, epitope-based vaccines rely on simple peptides that can be chemically synthesized. One of the major advantages of epitope-based vaccines is their reduced risk of allergenic reactions compared to traditional vaccines. This is because they do not contain the entire pathogen, only specific antigenic regions. Additionally, these vaccines are rapid, easy to design, and cost-effective, making them attractive candidates for vaccine development. While similar computational approaches have been successfully employed in the design of vaccines against other viruses such as SARS-CoV-2, Ebola, Zika, and Chikungunya, there are currently no commercial epitope-based vaccines on the market that have been developed using these bioinformatics approaches. This highlights the potential and importance of further research in this area to bring safe and effective epitope-based vaccines to the market for various infectious diseases, including dengue fever.

Methodology

Protein Sequence Retrieval

The amino acid sequences of the whole genome of the dengue virus serotypes (DENV1, DENV 2, DENV 3, DENV 4) were retrieved in FASTA format from the NCBI database (https://www.ncbi.nlm.nih.gov/) [24]. The entry number includes NC_001477, NC_001474, NC_001475, NC_002640 respectively.

B-Cell Epitope Prediction

B-cell epitopes for the four serotypes of dengue virus were predicted using the IEDB-B cell epitope prediction tool for the development of vaccine. The antigenecity scale of the Bipipred linear epitope prediction 2.0 prediction system was used to analyze the linear epitope prediction. The B cell epitope

were predicted using the IEDB resources (http://tools.iedb.org/main/) [25]. The retrieved sequence was submitted in prediction server. From the results, in B cell prediction the peptide sequence with the length <10 were choosed for further analysis.

T-Cell Epitope Prediction

T-cell epitope prediction was carried out using the IEDB MHC I binding prediction tool available at http://tools.iedb.org/main/ [26]. The retrieved protein sequence was submitted to the prediction server, and the analysis was performed across 77 different MHC class I alleles selected from the drop-down menu. Peptides were ranked based on their predicted binding affinity and those with a percentile rank of 1.1 or lower were selected as potential T-cell epitopes [27].

Antigenecity Prediction

The antigenicity scores, after filtering B-cell and T-cell epitopes (MHC classes I & II) according to their respective thresholds, were predicted using the VaxiJen 2.0 server. A threshold of 0.4 and above was used to select the epitopes based on their physicochemical properties [28]. To identify the most effective antigenic protein, the antigenic value of each protein was determined using the online prediction server VaxiJen v2.0, which is the first server for alignment-independent prediction of protective antigens. The protein containing the highest antigenic value was considered the most effective antigenic protein, based on the default parameters of the server.

Selection of Alleles

The selection of the MHC class I allele was necessary to minimize the number of epitopes before analyzing the 3D structures and the interactions between the alleles and the epitopes. Based on the results from the IEDB-MHC I epitope binding prediction tool, alleles that interacted with a higher number of epitopes were identified. Consequently, HLA-B57:01, HLA-B58:01, and HLA-B57:03 were found to interact with most of the predicted epitopes. The 3D structures of HLA-B57:01, HLA-B58:01, and HLA-B57:03 with PDB IDs 5VWJ, 6BXP, and 5VWD, respectively, were downloaded from the Protein Data Bank in PDB format [29].

Prediction of Peptide 3d Structure

Further, to enable docking studies and analyze the interactions between the epitopes and the alleles, the 3D structures of the epitopes were obtained using the PEP-FOLD 4.0 server, which suggests the best five predicted 3D structures of the peptide [30]. The best among the five structures were selected for further docking studies.

Molecular docking

To identify the most effective vaccine candidates, molecular docking of the selected MHC Class I interactive epitopes was performed using the ClusPro 2.0 server by evaluating the binding affinities and interactions between the

receptors and ligands [31]. Epitopes with the lowest binding energies were considered, as they exhibit greater interaction and stability.

Population Coverage Analysis

After predicting the most interactive epitopes with the help of ClusPro 2.0, population coverage analysis was performed for the selected epitope using the IEDB Population Coverage tool to assess the binding affinity of the epitopes to MHC Class I molecules against the global population coverage, based on the selection of HLA alleles corresponding to the respective epitope. A threshold of above 80% population coverage was considered for the selected epitope to qualify as an effective vaccine candidate [23].

Results

B-Cell Epitope Prediction and Antigenicity Prediction

B-cell epitopes for all four serotypes of the dengue virus were predicted from the whole genome of DENV using the IEDB BepiPred linear epitope prediction tool for vaccine development. The predicted B-Cell epitope for the four serotypes was shown in Table 1

Table 1 . IEDB result for B-Cell Epitope Prediction for DENV

Strain	Start	End	Peptide	Length	Antigen score
DENV 1	419	427	AWDFGSIGG	9	1.7867
	5	13	GIGSRDFVE	9	1.1016
	386	398	ALKLSWFKKGSSI	13	0.9637
DENV 2	420	427	WDFGSLGG	8	2.1175
	337	346	FEIMDLEKRH	10	2.07
	5	14	GISNREFKEG	10	1.6326
DENV 3	418	423	WDFGSV	6	3.043
	384	395	ALKINWYKKGSS	12	0.974
	48	53	TEATQL	6	0.6463
DENV 4	420	427	WDFGSVGG	8	2.24
	213	237	FLDLPLPWTTGADTLEVHWNHKERM	25	1.024
	6	12	VGNRDFV	7	0.9372

T cell epitope prediction (MHC class I) and antigenicity prediction

The T-cell epitopes were predicted using the IEDB resources (http://tools.iedb.org/main/). The retrieved sequence was submitted to the prediction server. In MHC class I, peptide sequences with a percentile rank of 1.1 were selected and shown in Table 2

Molecular Docking

The antigenicity score prediction and molecular docking were performed to identify the best epitopes of the Dengue fever virus for B-cell and MHC Class I alleles. The top 10 epitopes of MHC Class I and B-cell for each serotype (DENV-1, DENV-2, DENV-3, DENV-4), based on binding prediction scores of

1.1, were filtered and analyzed for antigenicity using the VaxiJen server. Molecular docking was then performed using the PDB, Pep-FOLD, and ClusPro servers. It was found that HLA-B58:01, HLA-B57:01, and HLA-B*57:03 were the most interactive alleles. The 3D structures of these alleles were viewed, and their corresponding PDB IDs were noted from the Protein Data Bank and are 5VWJ, 6BXP and 5VWD respectively (Figure 1).

Table 2. IEDB T-Cell (MHC Class I) Binding Prediction results of DENV and their Antigenicity Prediction

Strain	Allele	Start	End	Length	Peptide	Antigen score
DENV 1	HLA-A*11:01	463	471	9	LTWLGLNSR	2.334
	HLA-A*01:01	170	179	10	TTEIQLTDYG	1.8941
	HLA-A*68:02	472	480	9	STSLSMTCI	1.7774
DENV 2	HLA-A*68:01	315	323	9	TQHGTIVVR	1.3546
	HLA-A*68:01	462	471	10	VITWIGMNSR	1.3183
	HLA-A*02:01	199	207	9	LQMENKAWL	1.3181
DENV 3	HLA-B*08:01	467	475	9	NSKNTSMSF	1.9136
	HLA-A*30:01	316	325	10	GTILIKVEYK	1.8445
	HLA-A*24:02	455	463	9	IGIGVLLTW	1.4585
DENV 4	HLA-A*26:01	228	236	9	EVHWNHKER	2.1748
	HLA-A*03:01	226	234	9	TLEVHWNHK	2.0041
	HLA-A*26:01	228	237	10	EVHWNHKERM	1.7887

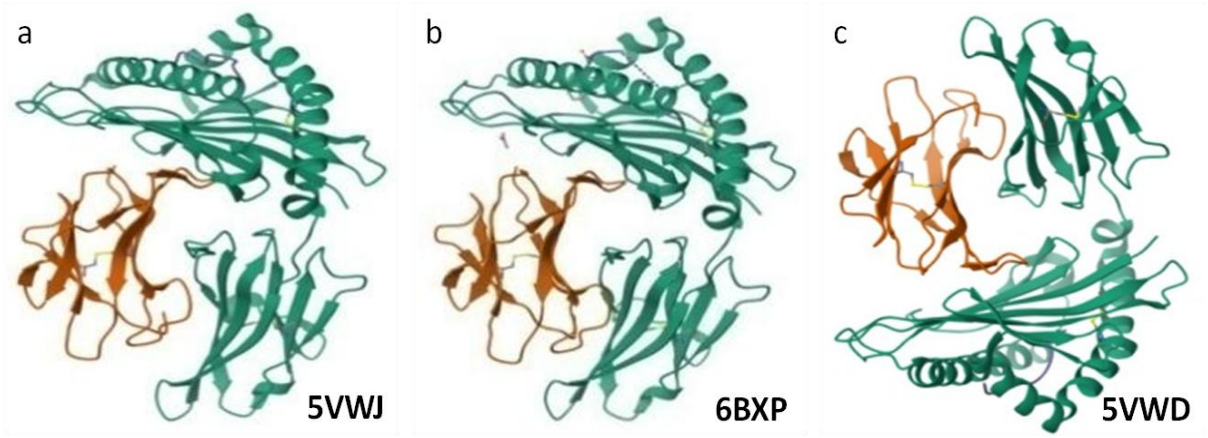

Figure 1. 3D structural representations of the most interactive HLA alleles identified in the study. (a) HLA-B58:01 (PDB ID: 5VWJ), (b) HLA-B57:01 (PDB ID: 6BXP), and (c) HLA-B*57:03 (PDB ID: 5VWD). The structures were retrieved from the Protein Data Bank (PDB) and visualized to assess epitope interactions.

The 3D structures of the 158 selected epitopes from the four serotypes of DENV were generated and downloaded using the Pep-Fold 4.0 server. Molecular docking was performed in ClusPro for the 158 selected epitopes separately, using the PDB IDs 5VWJ, 6BXP, and 5VWD of the selected alleles (receptors) and the downloaded 3D structures of the selected epitopes (ligands). The best docking scores for each epitope were noted, and the docking scores of all 158 selected epitopes were recorded. The docking images of the top epitope with the best (lowest energy) docking score in each

DENV serotype are displayed. The lowest docking scores indicate the most stable conformations of the molecules (Table 3). The best docking score from the top epitope was selected for each serotype (DENV-1, DENV-2, DENV-3, DENV-4) (Figure 2).

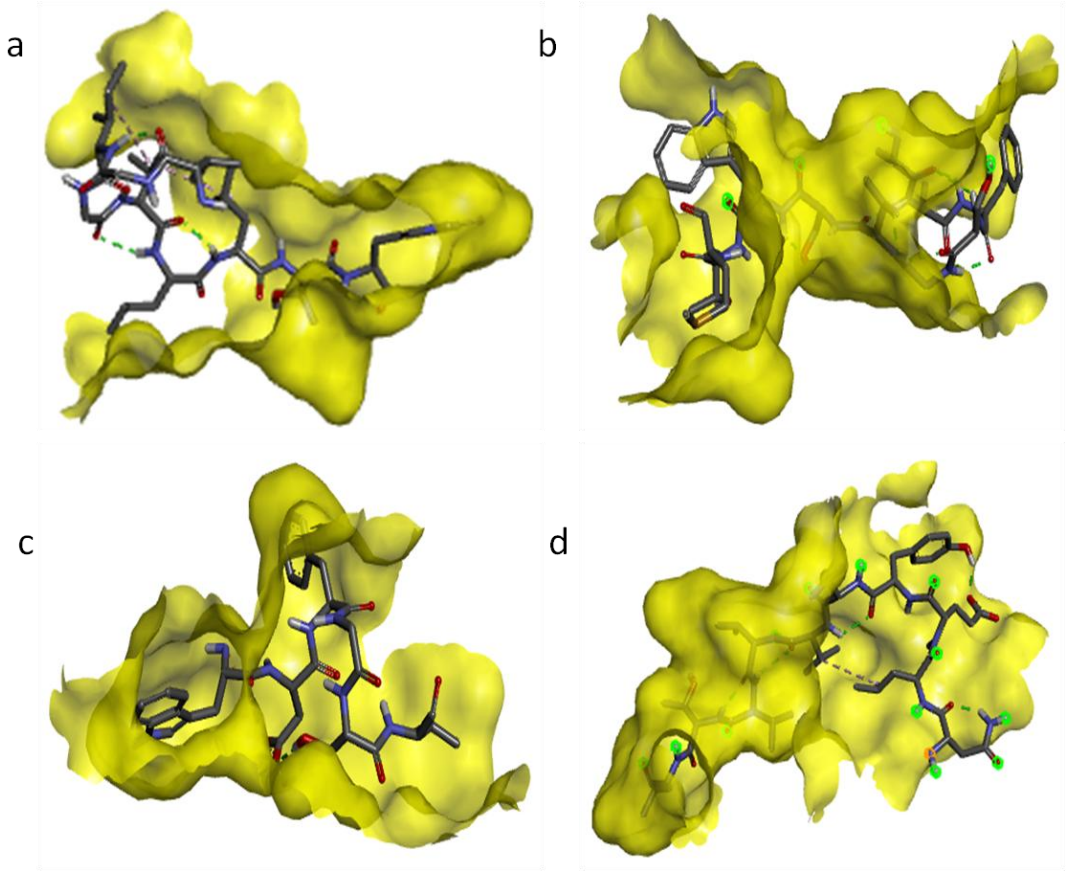

Figure 2: Molecular docking visualization of predicted epitopes from four Dengue virus serotypes with HLA alleles. (a) DENV-1 epitope IGIGVLLTW docked with HLA-B57:01, (b) DENV-2 epitope AAFSGVSWTM docked with HLA-B57:03, (c) DENV-3 epitope WDFGSV docked with HLA-B57:01, (d) DENV-4 epitope NLEYTVVVTV docked with HLA-B57:01. Yellow surfaces represent the molecular binding pocket of the HLA alleles, and the epitopes are shown as stick models interacting within the binding grooves.

Table 3. Docking score and antigen score of the selected Epitope

S.No	DENV	Allele	Epitope	Antigen Score	Docking Score (kcal/mol)
1	DENV 1	HLA - B*57:01	IGIGVLLTW	1.4585	-780.5
2	DENV 2	HLA - B*57:03	AAFSGVSWTM	1.1049	-755.2
3	DENV 3	HLA - B*57:01	WDFGSV	3.043	-607.4
4	DENV 4	HLA - B*57:01	NLEYTVVVTV	1.4111	-936.1

Population Coverage Analysis

After predicting the most interactive epitopes with the help of ClusPro 2.0, the population coverage analysis was done for the selected epitopes peptides IGIGVLLTW, AAFSGVSWTM, WDFGSV, NLEYTVVVTV using the IEDB-Population coverage tool to access the binding affinity of the epitopes to MHC

Class I & Class II molecules against the coverage of world population via selection of HLA alleles of the respective epitopes. The threshold for population coverage analysis is considered to above 80% for the selected epitope to be an effective vaccine candidate. But, the resultant population coverage for all the 4 epitopes were found to be 98.96% (Figure 3) which indicates that the predicted epitopes are having high binding affinity to the MHC class I and MHC class II molecules against the world population coverage

MHC class	Coverage	Average hit	PC90
combined	98.47%	2.82	1.72

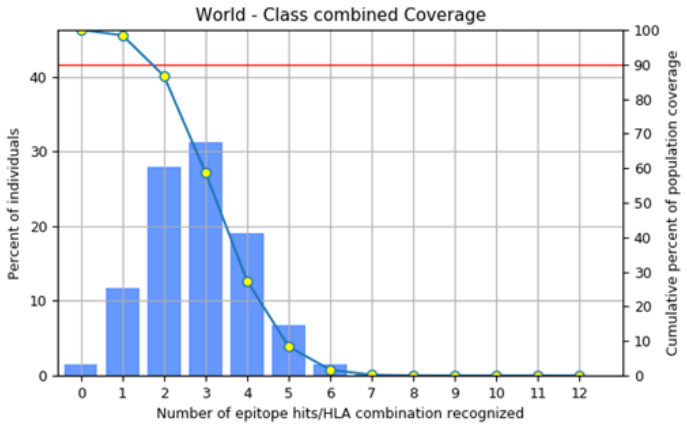

Figure 3. Population coverage analysis of selected T-cell epitopes based on global HLA allele distribution. The histogram shows the percentage of individuals (left Y-axis) recognizing different numbers of epitope/HLA combinations (X-axis), while the line graph represents the cumulative percentage of population coverage (right Y-axis). The analysis indicates a combined MHC class coverage of 98.47%**,** with an average epitope hit of 2.82 per individual and a PC90 value of 1.72**,** meaning 90% of the population is expected to recognize at least 1.72 epitope-HLA combinations.

Discussion

An efficient vaccination strategy capable of inducing protective antibodies against all four serotypes of the dengue virus is imperative. In recent years, bioinformatics has significantly accelerated drug development processes. This study focuses on the concept of "Epitope-based peptide vaccine design," which offers a more systematic approach compared to conventional methods that are often slow and reliant on random antigen selection. The research aims to identify potential vaccine candidates against the Epstein-Barr virus (EBV) through the prediction of immunogenic peptide sequences and assessment of their antigenicity.

We have focused on polyproteins as targets for epitope prediction due to their pivotal roles in viral attachment, fusion, and entry, rendering them promising candidates for vaccine development. Using the Immune Epitope Database (IEDB), we predicted both B cell and T cell epitopes. For B cell

epitopes, we selected peptide sequences ranging from 11 to 16 amino acids in length. In predicting T cell epitopes, we focused on MHC I. Specifically, we chose peptide sequences that scored 1.1 with lengths between 8 and 14 amino acids. This approach enables the proposal of a more precise vaccine design based on both B cell Epitopes (BCE) and T cell Epitopes (TCE). We further assessed the antigenicity of these B and T cell peptide sequences using the Vaxijen Server. Our analysis led to the prediction of 26 antigenic peptide sequences for B cells across all four serotypes, and 122 antigenic peptide sequences for MHC I across the four serotypes.

Utilizing ClusPro for molecular docking, we conducted predictions to elucidate the binding interactions between epitopes and human HLA alleles [5VWD, 5VWJ, 6BXP]. Following ClusPro analysis, we identified peptides with the lowest binding affinity for each human allele and subsequently validated their structures. Our findings unveil promising vaccine candidates, including peptides from the whole genomes of all four dengue virus serotypes: DENV1 (IGIGVLLTW), DENV2 (AAFSGVSWTM), DENV3 (WDFGSV), and DENV4 (NLEYTVVVTW). For an epitope to be considered an effective vaccine candidate, the threshold for population coverage analysis is typically set above 80%. However, our analysis demonstrated a resultant population coverage of 98.96% for all four epitopes, indicating their high binding affinity to MHC class I and MHC class II molecules across the global population.

Conclusion

In this study, we employed a modern computational approach to vaccine design, which offers increased efficiency, reduced time, cost-effectiveness, and enhanced specificity. Through our investigation, we successfully identified several DENV polyproteins isolated from diverse regions of the world population. The predicted antigenic epitopes hold potential for the development of an effective vaccine to prevent further outbreaks of the Dengue virus. By utilizing bioinformatics tools, we have proposed and designed a suitable epitope that could lead to a successful vaccine against Dengue Virus. Our findings highlight promising vaccine candidates, including peptides from the whole genomes of all four Dengue virus serotypes: DENV1 (IGIGVLLTW), DENV2 (AAFSGVSWTM), DENV3 (WDFGSV), and DENV4 (NLEYTVVVTW). Importantly, the population coverage analysis revealed a high coverage of 98.96% for all four epitopes, indicating their potential effectiveness as vaccines against the Dengue virus.

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